156. A DNA molecule according to Claim 139 that is double stranded.

REMARKS

Claims 1, 26-31, 33, 36, 37, 39, 40, 44-46, and 50-138 have been canceled. Claims 139-156 have been added. Support for the newly added claims can be found in the specification (see at least page 2, lines 19-24; page 4, lines 11-23; page 5, lines 5-12; and page 10, line 20-page 16, line 10 (Examples 1-5)).

It is respectfully submitted that the outstanding rejections and/or objection are moot in view of the cancellation of the previously pending claims. For the purpose of expediting prosecution of the above-identified application, the outstanding objection and rejections will be discussed below as they pertain to the newly added claims. It should in no way be construed as an acquiescence to an objection or rejection if it is not discussed below.

Request that the Present Amendment be Considered as an Amendment Submitted Prior to a Final Rejection

It is respectfully requested that the present amendment be considered as an amendment submitted prior to a final rejection. The finality of the outstanding office action is improper and should be withdrawn.

It is respectfully submitted that Applicants' amendment did not necessitate the new grounds of rejection and that the previous amendments to the claims did not "effectively change the invention previously examined". The language "stabilized against cellular recombination" was removed from a previously pending dependent claim (see claim 25 (filed by Applicants as claim 2 but renumbered by the Examiner as claim 25) which was filed in a preliminary amendment on October 26, 1993 and which was canceled in the last amendment) and inserted into independent claim 1. This language

was not introduced into the claims for the first time in the last amendment. The "new rejections" made in the outstanding office action over the language "stabilized against cellular recombination" should have been made over previously pending dependent claim 25 which would have given applicants an opportunity to respond to the rejections prior to a final rejection.

It is respectfully requested that the present amendment be considered as an amendment submitted prior to a final rejection because the finality of the last office action was premature. It is further submitted that the new grounds of rejection were not necessitated by amendment and could have been made over previously pending dependent claim 25 which was added by preliminary amendment on October 26, 1993.

Applicants' Invention

Applicants' presently claimed invention is based, at least in part, on the recognition that a substantial and unresolved problem existed in the maintenance of cystic fibrosis transmembrane conductance regulator-encoding (CFTR-encoding) DNA molecules in bacterial cells (see at least lines 11-24 of page 4 of the specification). The problem was discussed throughout the specification of the above-identified application and is not being raised for the first time in the present amendment. Indeed, recognition and resolution of this problem has been central to the production of a stable, full length CFTR-encoding DNA. Applicants have resolved the art-recognized difficulties in recovering from bacterial cells clones encoding full length CFTR polypeptides(see at least pages 10-11 of the specification- Example 1). The DNA molecules were not being stably maintained in bacterial cells, and the Applicants successfully determined that inadvertent expression of polypeptides derived from CFTR encoding DNA was occurring. The inadvertently expressed CFTR-derived polypeptides were determined to be toxic to bacterial cells used for propagation/maintenance, leading to a situation where clones encoding full length

CFTR polypeptides were not recoverable. Applicants further realized that intrinsic DNA clone instability was not responsible for the art-recognized failure to recover bacterial clones containing full length encoding DNA.

Applicants' medically important invention comprises, in part, a development of several approaches to facilitate maintenance of a full length CFTR-encoding DNA in bacterial cells therefore overcoming the aforementioned unresolved, scientific hurdle. These approaches included (1) the use of a low copy number plasmid in host bacterial cells or (2) the use of a sequence modification in the CFTR-encoding sequence itself, e.g. the insertion of an intron or point mutation. These approaches were designed to reduce the inadvertent expression of polypeptides derived from the CFTR-encoding DNA. See at least Examples 1-5 of the specification. These approaches were designed to facilitate the maintenance of CFTR-encoding DNA molecules in bacterial cells by allowing propagation and maintenance to occur such that clones encoding full length CFTR polypeptides were recoverable and are useful, for example, for transforming other cells.

The invention encompassed by the newly added claims includes a DNA molecule that encodes for CFTR polypeptides but containing also a sequence modification, e.g. intron or point mutation (see claims 139-150 and 155). The presence of the sequence modification within the encoding sequence of the DNA molecule facilitates maintenance of the molecule in a host bacterial cell. The invention also includes a DNA molecule consisting essentially of: (1) a DNA sequence encoding for a polypeptide having an amino acid sequence sufficiently duplicative of that of cystic fibrosis transmembrane conductance regulator to allow possession of the biological property of epithelial cell anion channel regulation, and (2) one or more regulatory elements operatively linked thereto. The DNA molecule can be maintained stably in a culture of viable host bacterial cells and be recovered in purified form (see claims 150-154). The presently claimed DNA molecules can be stably maintained and propagated in bacterial cells and

subsequently the molecules can be used to transform other cells, e.g. mammalian cells, resulting in expression of the CFTR polypeptide.

Telephonic Interview

The telephonic interview between Examiner Carlson and the undersigned on August 4, 1994 is gratefully acknowledged. The rejections set forth in the outstanding office action along with various forms of claim language were discussed during the interview. The finality of the last office action also was discussed. It is understood that Examiner Carlson agreed that if the language that was newly rejected had merely been moved from a dependent claim to an independent claim then a new ground of rejection over such language would not have been necessitated by applicants' amendment

Rejection Under 35 U.S.C. 102(e) as Anticipated by or, in the Alternative Under 35 U.S.C. 103 as Obvious Over Collins et al. (USP 5,240,846)

Claims 36, 37, 46, 55-57, and 62-64 were rejected under 35 U.S.C 102(e) as being "anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Collins et al. (USP 5,240,846)." Particularly, the Examiner states that "Collins et al. teach vectors for the expression of the CFTR gene to be used for gene therapy" and "Collins et al. deliver and express a single normal copy of the CFTR gene and this corrects the chloride regulatory defect in human colon tumor cell lines". It is further the Examiner's position that "Collins et al. teach to place the DNA encoding CFTR into low copy vectors to prevent cell death during expression of CFTR (col. 2)".

This rejection will be discussed as it pertains to the newly added claims. As discussed above, the newly added claims are drawn to DNA molecules which encode CFTR and which contain a sequence modification which facilitates maintenance of the molecules in bacterial host cells. It is respectfully submitted that Collins et al. is not

available as a reference against the presently pending claims. The portions of the issued patent which pertain to "methods of stabiliz[ing] the full-length CFTR cDNA", e.g., the introduction of silent mutations into the gene to stabilize cloning, were introduced into the file of the Collins application only as of September 18, 1990 (see the file history of USSN 07/584,275 in comparison to the text of the earlier filed applications to which Collins claims priority - in this regard see at least column 3, lines 7-8 ;column 7, line 55-column 8, line 31; and column 11, line 15-56 of the issued Collins patent). The filing date of the '275 application is more than six months after the effective original filing date (March 5, 1990, USSN 07/488,307 of the present Applicants) for the subject matter in the present application and therefore any rejection of the presently pending claims over Collins et al. would be improper.

Applicant's further traverse and request that the Examiner clarify her statement that "Collins et al. teach to place the DNA encoding CFTR into low copy vectors to prevent cell death during expression of CFTR (col. 2)". Applicants have reviewed the issued patent including the cited column and cannot locate such a teaching.

Rejection Under 35 U.S.C. 102(a) as Anticipated by or, in the Alternative, Under 35 U.S.C. 103 as Obvious Over Riordan et al.

Claims 26, 55-57, and 62-64 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Riordan et al. Particularly, the Examiner states that "Riordan et al. cloned the CFTR gene from epithelial cells to determine the role of Phe508 in CF" and "[m]ost of the cDNA isolated contained sequence insertions corresponding to introns (page 1067, col. 1)". Particularly, the Examiner states that "the cDNA taught by Riordan et al. is 99% identical to that disclosed by the Applicants in Table 1".

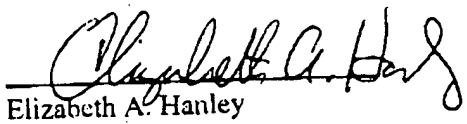
This rejection will be discussed as it pertains to the newly added claims. As discussed above, the newly added claims are drawn to DNA molecules which encode CFTR and which contain a sequence modification which facilitates maintenance of the molecules in bacterial host cells. Riordan et al. did not teach the existence of or suggest the solution to the fundamental problem recognized by the present Applicants which is the art-recognized inability to recover clones encoding full length CFTR polypeptides from bacterial cells.

SUMMARY

The above rejections and objections are either improper or do not pertain to the newly added claims and should be withdrawn. The claims are believed to be in condition for allowance.

If a telephone conversation with applicant's attorney would expedite the prosecution of the above-identified application, the examiner is urged to call applicant's attorney at (617) 227-7400.

Respectfully submitted,



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